

**Last Approved Labeling Text
Package Circular**



9090701

PROPECIA^{*}

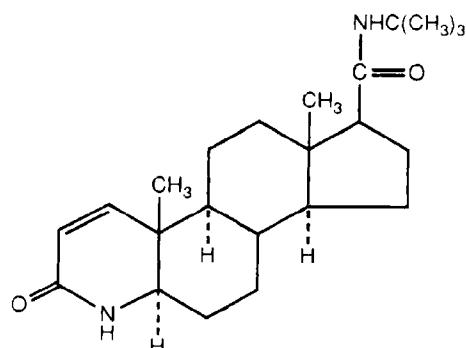
(Finasteride)

Tablets, 1 mg

DESCRIPTION

PROPECIA^{*} (finasteride), a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5 α -reductase, an intracellular enzyme that converts the androgen testosterone into 5 α -dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-,(5 α ,17 β)-. The empirical formula of finasteride is C₂₃H₃₆N₂O₂ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water.

PROPECIA tablets for oral administration are film-coated tablets that contain 1 mg of finasteride and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, hydroxypropyl methylcellulose 2910, hydroxypropyl cellulose, titanium dioxide, talc, yellow ferric oxide, and red ferric oxide.

CLINICAL PHARMACOLOGY

Finasteride is a competitive and specific inhibitor of Type II 5 α -reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5 α -reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5 α -reductase is responsible for approximately one-third of circulating DHT. The Type II 5 α -reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5 α -reductase over Type I isozyme (IC₅₀=500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibition by finasteride is accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP+. The turnover for the enzyme complex is slow (t_{1/2} approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5 α -reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1-mg tablet.

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In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. The relative contributions of these reductions to the treatment effect of finasteride have not been defined. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

Finasteride had no effect on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, nor did it affect the plasma lipid profile (e.g., total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) or bone mineral density. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH) or follicle-stimulating hormone (FSH) were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone, indicating that the hypothalamic-pituitary-testicular axis was not affected. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

Pharmacokinetics

Following an oral dose of ¹⁴C-finasteride in man, a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces. The major compound isolated from urine was the monocarboxylic acid metabolite; virtually no unchanged drug was recovered. The t-butyl side chain monohydroxylated metabolite has been isolated from plasma.

These metabolites possessed no more than 20% of the 5 α -reductase inhibitory activity of finasteride.

In a study in 15 healthy male subjects, the mean bioavailability of finasteride 1-mg tablets was 65% (range 26-170%), based on the ratio of AUC relative to a 5-mg intravenous dose infused over 60 minutes. Following intravenous infusion, mean plasma clearance was 165 mL/min (range, 70-279 mL/min) and mean steady-state volume of distribution was 76 liters (range, 44-96 liters). In a separate study, the bioavailability of finasteride was not affected by food.

Approximately 90% of circulating finasteride is bound to plasma proteins. Finasteride has been found to cross the blood-brain barrier.

There is a slow accumulation phase for finasteride after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9-13.7 ng/mL) and was reached 1 to 2 hours postdose; AUC_(0-24 hr) was 53 ng·hr/mL (range, 20-154 ng·hr/mL) and mean terminal half-life of elimination was 4.8 hours (range, 3.3-13.4 hours).

Semen levels have been measured in 35 men taking finasteride 1 mg daily for 6 weeks. In 60% (21 of 35) of the samples, finasteride levels were undetectable. The mean finasteride level was 0.26 ng/mL and the highest level measured was 1.52 ng/mL. Using this highest semen level measured and assuming 100% absorption from a 5-mL ejaculate per day, human exposure through vaginal absorption would be up to 7.6 ng per day, which is 750 times lower than the exposure from the no-effect dose for developmental abnormalities in Rhesus monkeys (see PRECAUTIONS, *Pregnancy*).

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age. These findings are of no clinical significance, and a reduction in dosage in the elderly is not warranted.

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment (creatinine clearance ranging from 9.0 to 55 mL/min), the values for AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ¹⁴C-finasteride were similar to those obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). Furthermore, finasteride has been well tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

Clinical Studies

The efficacy of PROPECIA was demonstrated in men (88% Caucasian) with mild to moderate androgenetic alopecia (male pattern hair loss) between 18 and 41 years of age. In order to prevent seborrheic dermatitis which might confound the assessment of hair growth in these studies (controlled phase and extensions), all men, whether treated with finasteride or placebo, were instructed to use a specified, medicated, tar-based shampoo (Neutrogena T/Gel®** Shampoo).

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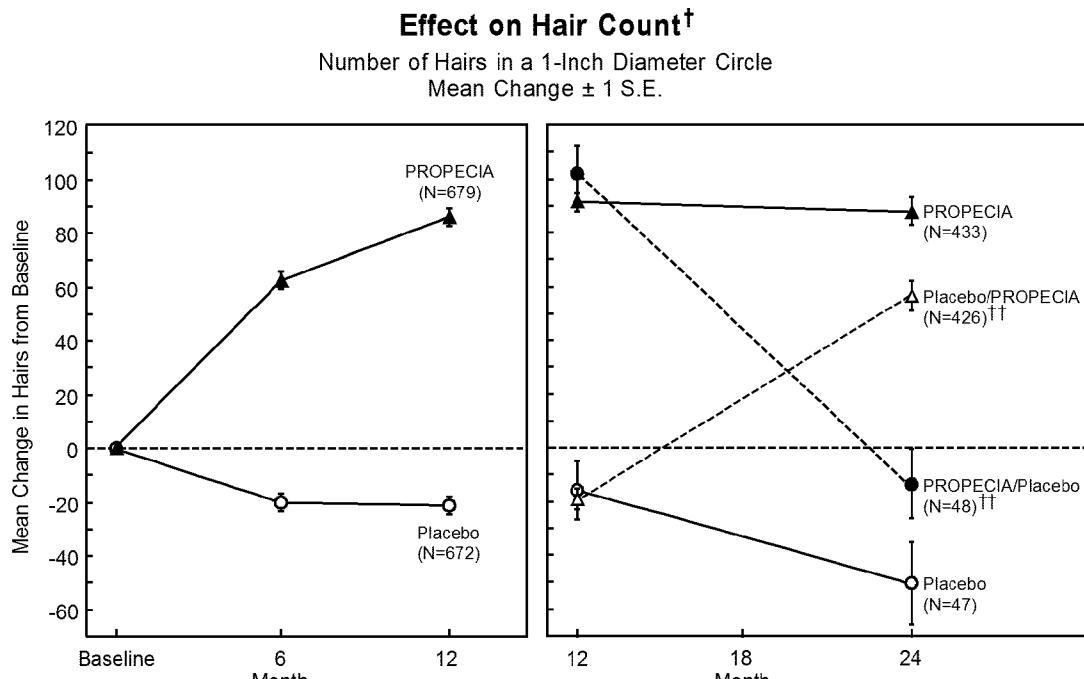
There were three double-blind, randomized, placebo-controlled studies of 12-month duration. The two primary endpoints were hair count and patient self-assessment; the two secondary endpoints were investigator assessment and ratings of photographs. The three studies were conducted in 1,879 men with mild to moderate, but not complete, hair loss. Two of the studies enrolled men with predominantly mild to moderate vertex hair loss (n=1,553). The third enrolled men having mild to moderate hair loss in the anterior mid-scalp area with or without vertex balding (n=326).

Two studies on Vertex Baldness

Of the men who completed the first 12 months of the two vertex baldness trials, 1,215 elected to continue in double-blind, placebo-controlled, 12-month extension studies. There were 547 men receiving PROPECIA for both the initial and extension periods (up to 24 months) and 60 men receiving placebo for the same periods. In addition, there were 65 men who received PROPECIA for the initial 12 months followed by placebo in the 12-month extension period, and 543 men who received placebo for the initial 12 months followed by PROPECIA in the 12-month extension period (See Figure below).

Hair counts were assessed by photographic enlargements of a representative area of active hair loss. In these two studies in men with vertex baldness, significant increases in hair count were demonstrated at 6 and 12 months in men treated with PROPECIA, while significant hair loss from baseline was demonstrated in those treated with placebo. At 12 months there was a 107-hair difference from placebo ($p<0.001$, PROPECIA [n=679 evaluable men] vs placebo [n=672 evaluable men]) within a 1-inch diameter circle (5.1 cm^2). Hair count was maintained in those men taking PROPECIA (n=433 evaluable men) for up to 24 months, while the placebo group (n=47 evaluable men) continued to show progressive hair loss. At 24 months, this resulted in a 138-hair difference between treatment groups ($p<0.001$) within the same area. Patients who switched from placebo to PROPECIA (n=426 evaluable men) at the end of the initial 12 months had an increase in hair count at 24 months. A change of treatment from PROPECIA to placebo (n=48 evaluable men) at the end of the initial 12 months resulted in reversal of the increase in hair count 12 months later, at 24 months. See figure below for combined study results.

At 12 months, 14% of men treated with PROPECIA had hair loss (defined as any decrease in hair count from baseline) compared with 58% of men in the placebo group. In men treated for up to 24 months, 17% of those treated with PROPECIA demonstrated hair loss compared with 72% of those in the placebo group.



[†] Pooled data from vertex hair loss studies (mean baseline hair count = 876)

^{††} At the end of initial 12-month period, treatment switched from PROPECIA to placebo (----- PROPECIA/Placebo) or from placebo to PROPECIA (----- Placebo/PROPECIA).

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Patient self-assessment was obtained at each clinic visit from a self-administered questionnaire, which included questions on their perception of hair growth, hair loss, and appearance. This self-assessment demonstrated an increase in amount of hair, a decrease in hair loss, and improvement in appearance in men treated with PROPECIA. Overall improvement compared with placebo was seen as early as 3 months ($p<0.05$), with continued improvement over 24 months.

Investigator assessment was based on a 7-point scale evaluating increases or decreases in scalp hair at each patient visit. This assessment showed significantly greater increases in hair growth in men treated with PROPECIA compared with placebo as early as 3 months ($p<0.001$). At 12 months, the investigators rated 65% of men treated with PROPECIA as having increased hair growth compared with 37% in the placebo group. At 24 months, the investigators rated 80% of men treated with PROPECIA as having increased hair growth compared with 47% of men treated with placebo.

Standardized photographs of the head were assessed in a blinded fashion, at the beginning of the study and at 6, 12, 18 and 24 months. An independent panel rated increases or decreases in scalp hair on the same 7-point scale as the investigator assessment. At 12 months, 48% of men treated with PROPECIA had an increase as compared with 7% of men treated with placebo. At 24 months, an increase in hair growth was demonstrated in 66% of men treated with PROPECIA compared with 7% of men treated with placebo. Based on this assessment, continued treatment with PROPECIA resulted in further improvement. These results were observed in the context of no further increase in hair count between month 12 and month 24.

In one of the two vertex baldness studies, patients were questioned on non-scalp body hair growth. PROPECIA did not appear to affect non-scalp body hair.

Study on Hair Loss in the Anterior Mid-Scalp Area

A third study of 12-month duration, designed to assess the efficacy of PROPECIA in men with hair loss in the anterior mid-scalp area, also demonstrated significant increases in hair count compared with placebo. Increases in hair count were accompanied by improvements in patient self-assessment, investigator assessment, and ratings based on standardized photographs. Hair counts were obtained in the anterior mid-scalp area, and did not include the area of bitemporal recession or the anterior hairline.

Summary of Clinical Studies

Clinical studies were conducted in men aged 18 to 41 with mild to moderate degrees of androgenetic alopecia. All men treated with PROPECIA or placebo received a tar-based shampoo (Neutrogena T/Gel®** Shampoo). Clinical improvement was seen as early as 3 months in the patients treated with PROPECIA and led to a net increase in scalp hair count and hair regrowth. In addition, clinical studies demonstrated slowing of hair loss with PROPECIA by patient self-assessment. These effects were maintained through the second year of treatment. Maintenance of or improvement in clinical efficacy has also been demonstrated in controlled and open-extension studies for up to 3 years.

Ethnic Analysis of Clinical Data

In a combined analysis of the two studies on vertex baldness, mean hair count changes from baseline were 91 vs -19 hairs (PROPECIA vs placebo) among Caucasians ($n=1,185$), 49 vs -27 hairs among Blacks ($n=84$), 53 vs -38 hairs among Asians ($n=17$), 67 vs 5 hairs among Hispanics ($n=45$) and 67 vs -15 hairs among other ethnic groups ($n=20$). Patient self-assessment showed improvement across racial groups with PROPECIA treatment, except for satisfaction of the frontal hairline and vertex in Black men, who were satisfied overall.

A sexual function questionnaire was self-administered by patients participating in the two vertex baldness trials to detect more subtle changes in sexual function. At Month 12, statistically significant differences in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems). However, no significant difference was seen in the question on overall satisfaction with sex life.

INDICATIONS AND USAGE

PROPECIA is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY**. Safety and efficacy were demonstrated in men between 18 to 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area (See CLINICAL PHARMACOLOGY, *Clinical Studies*).

Efficacy in bitemporal recession has not been established.

PROPECIA is not indicated in women (see CONTRAINDICATIONS).

PROPECIA is not indicated in children (see PRECAUTIONS, *Pediatric Use*).

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CONTRAINDICATIONS

PROPECIA is contraindicated in the following:

Pregnancy. Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of 5 α -reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See also **WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, Information for Patients and Pregnancy.**) In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

Hypersensitivity to any component of this medication.

WARNINGS

PROPECIA is not indicated for use in pediatric patients (See **INDICATIONS AND USAGE; and PRECAUTIONS, Pediatric Use**) or women (See also **PRECAUTIONS, Information for Patients and Pregnancy; and HOW SUPPLIED, Storage and Handling**).

EXPOSURE OF WOMEN - RISK TO MALE FETUS

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also **CONTRAINDICATIONS; PRECAUTIONS, Information for Patients and Pregnancy; and HOW SUPPLIED, Storage and Handling.**)

PRECAUTIONS*General*

Caution should be used in the administration of PROPECIA in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

Information for Patients

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also **CONTRAINDICATIONS; WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; PRECAUTIONS, Pregnancy; and HOW SUPPLIED, Storage and Handling.**)

See also Patient Package Insert.

Drug/Laboratory Test Interactions

In clinical studies with PROPECIA in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at Month 12. When finasteride is used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Until further information is gathered in men >41 years of age without BPH, consideration should be given to doubling the PSA level in men undergoing this test while taking PROPECIA.

Drug Interactions

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing enzyme system. Compounds that have been tested in man include antipyrine, digoxin, propranolol, theophylline, and warfarin and no interactions were found.

Other concomitant therapy: Although specific interaction studies were not performed, finasteride doses of 1 mg or more were concomitantly used in clinical studies with acetaminophen, α -blockers, analgesics, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H₂ antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolone anti-infectives without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses

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produced respective systemic exposure in rats of 888 and 2,192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated AUC_(0-24 hr) for animals and mean AUC_(0-24 hr) for man (0.05 µg·hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (1,824 times the human exposure). In mice at a dose of 25 mg/kg/day (184 times the human exposure, estimated) and in rats at a dose of ≥ 40 mg/kg/day (312 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (240 and 2,800 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (18.4 times the human exposure).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, when Chinese hamster ovary cells were treated with high concentrations (450-550 µmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 18,000-22,000 times the peak plasma levels in man given a total dose of 1 mg. Further, the concentrations (450-550 µmol) used in *in vitro* studies are not achievable in a biological system. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (1,824 times the human exposure, estimated) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4,344 times the estimated human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (488 times the estimated human exposure), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats but is not relevant in man.

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS.

PROPECIA is not indicated for use in women.

Administration of finasteride to pregnant rats at doses ranging from 100 µg/kg/day to 100 mg/kg/day (5-5,000 times the recommended human dose of 1 mg/day) resulted in dose-dependent development of hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at ≥ 30 µg/kg/day (≥ 1.5 times the recommended human dose of 1 mg/day) and decreased anogenital distance when given finasteride at ≥ 3 µg/kg/day (one-fifth the recommended human dose of 1 mg/day). The critical period during which these effects can be induced in male rats has been defined to be days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5 α -reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5 α -reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 488 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (150 times the recommended human dose of 1 mg/day) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring. No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day (5000 times the recommended human dose of 1 mg/day). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

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The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 100 times the recommended human dose of 1 mg/day or approximately 12 million times the highest estimated exposure to finasteride from semen of men taking 1 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

Nursing Mothers

PROPECIA is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

Pediatric Use

PROPECIA is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical Studies for PROPECIA (finasteride 1 mg) in the Treatment of Male Pattern Hair Loss

In controlled clinical trials for PROPECIA of 12-month duration, 1.4% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo); 1.2% of patients on PROPECIA and 0.9% of patients on placebo discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in $\geq 1\%$ of patients treated for 12 months with PROPECIA or placebo, respectively: decreased libido (1.8%, 1.3%), erectile dysfunction (1.3%, 0.7%) and ejaculation disorder (1.2%, 0.7%; primarily decreased volume of ejaculate:[0.8%, 0.4%]). Integrated analysis of clinical adverse experiences showed that during treatment with PROPECIA, 36 (3.8%) of 945 men had reported one or more of these adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo ($p=0.04$). Resolution occurred in all men who discontinued therapy with PROPECIA due to these side effects and in 58% of those who continued therapy.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 mL (-11%) compared with 0.2 mL (-8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that finasteride at 5 times the dosage of PROPECIA (5 mg daily) produced significant median decreases of approximately 0.5 mL (-25%) compared to placebo in ejaculate volume but this was reversible after discontinuation of treatment.

In the clinical studies with PROPECIA, the incidences for breast tenderness and enlargement, and for hypersensitivity reactions in finasteride-treated patients were not different from those in patients treated with placebo.

Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR (finasteride 5 mg) in the Treatment of Benign Prostatic Hyperplasia*

In controlled clinical trials for PROSCAR of 12-month duration, 1.3% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (0.9% for placebo); only one patient on PROSCAR (0.2%) and one patient on placebo (0.2%) discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in $\geq 1\%$ of patients treated for 12 months with PROSCAR or placebo, respectively: erectile dysfunction (3.7%, 1.1%), decreased libido (3.3%, 1.6%) and decreased volume of ejaculate (2.8%, 0.9%). The adverse experience profiles for patients treated with finasteride 1 mg/day for 12 months and those maintained on PROSCAR for 24 to 48 months were similar to that observed in the 12-month controlled studies with PROSCAR. Sexual adverse experiences resolved with continued treatment in over 60% of patients who reported them.

Adverse Effects Reported in Post-Marketing Experience for PROSCAR (finasteride 5 mg)

Breast tenderness and enlargement, as well as hypersensitivity reactions, including lip swelling and skin rash have been reported.

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OVERDOSAGE

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions. Until further experience is obtained, no specific treatment for an overdose with finasteride can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1,500 mg/m² (500 mg/kg) and in female and male rats at single oral doses of 2,360 mg/m² (400 mg/kg) and 5,900 mg/m² (1,000 mg/kg), respectively.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg once a day.

PROPECIA may be administered with or without meals.

In general, daily use for three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit. Withdrawal of treatment leads to reversal of effect within 12 months.

HOW SUPPLIED

No. 6550 — PROPECIA tablets, 1 mg, are tan, octagonal, film-coated convex tablets with code MRK 71 on one side and PROPECIA 1 on the other. They are supplied as follows:

NDC 0006-0071-31 unit of use bottles of 30

NDC 0006-0071-61 ProPak · ** - carton of 3 unit of use bottles of 30.

Storage and Handling

Store at room temperature, 15-30°C (59-86°F). Keep container closed and protect from moisture.

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed. (See WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, *Information for Patients and Pregnancy*.)



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**Last Approved Labeling Text
Patient Product Insert**

9090801

PROPECIA · *
(Finasteride) Tablets
Patient Information about
PROPECIA · (Pro-pee-sha)
Generic name: finasteride
(fin-AS-tur-eyed)

PROPECIA ** is for use by MEN ONLY.

Please read this leaflet before you start taking PROPECIA. Also, read the information included with PROPECIA each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss PROPECIA when you start taking your medication and at regular checkups.

What is PROPECIA used for?

PROPECIA is used for the treatment of male pattern hair loss on the vertex and the anterior mid-scalp area.

PROPECIA is for use by **MEN ONLY** and should **NOT** be used by women or children.

What is male pattern hair loss?

Male pattern hair loss is a common condition in which men experience thinning of the hair on the scalp. Often, this results in a receding hairline and/or balding on the top of the head. These changes typically begin gradually in men in their 20s.

Doctors believe male pattern hair loss is due to heredity and is dependent on hormonal effects. Doctors refer to this type of hair loss as androgenetic alopecia.

Results of clinical studies:

For 12 months, doctors studied over 1800 men aged 18 to 41 with mild to moderate amounts of ongoing hair loss. All men, whether receiving PROPECIA or placebo (a pill containing no medication) were given a medicated shampoo (Neutrogena T/Gel® *** Shampoo). Of these men, approximately 1200 with hair loss at the top of the head were studied for an additional 12 months. In general, men who took PROPECIA maintained or increased the number of visible scalp hairs and noticed improvement in their hair in the first year, with the effect maintained in the second year. Hair counts in men who did not take PROPECIA continued to decrease.

In one study, patients were questioned on the growth of body hair. PROPECIA did not appear to affect hair in places other than the scalp.

Will PROPECIA work for me?

For most men, PROPECIA increases the number of scalp hairs, helping to fill in thin or balding areas of the scalp. Men taking PROPECIA noted a slowing of hair loss during two years of use. Although results

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PROPECIA · (Finasteride) Tablets

9090801

will vary, generally you will not be able to grow back all of the hair you have lost. There is not sufficient evidence that PROPECIA works in the treatment of receding hairline in the temporal area on both sides of the head.

Male pattern hair loss occurs gradually over time. On average, healthy hair grows only about half an inch each month. Therefore, it will take time to see any effect.

You may need to take PROPECIA daily for three months or more before you see a benefit from taking PROPECIA. PROPECIA can only work over the long term if you continue taking it. If the drug has not worked for you in twelve months, further treatment is unlikely to be of benefit. If you stop taking PROPECIA, you will likely lose the hair you have gained within 12 months of stopping treatment. You should discuss this with your doctor.

How should I take PROPECIA?

Follow your doctor's instructions.

- | Take one tablet by mouth each day.
- | You may take PROPECIA with or without food.
- | If you forget to take PROPECIA, do not take an extra tablet. Just take the next tablet as usual.

PROPECIA will not work faster or better if you take it more than once a day.

Who should NOT take PROPECIA?

- | PROPECIA is for the treatment of male pattern hair loss in **MEN ONLY** and should not be taken by women or children.
- | Anyone allergic to any of the ingredients.

A warning about PROPECIA and pregnancy.

- | **Women who are or may potentially be pregnant:**
 - must not use PROPECIA
 - should not handle crushed or broken tablets of PROPECIA.

If a woman who is pregnant with a male baby absorbs the active ingredient in PROPECIA, either by swallowing or through the skin, it may cause abnormalities of a male baby's sex organs. If a woman who is pregnant comes into contact with the active ingredient in PROPECIA, a doctor should be consulted. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

What are the possible side effects of PROPECIA?

Like all prescription products, PROPECIA may cause side effects. In clinical studies, side effects from PROPECIA were uncommon and did not affect most men. A small number of men experienced certain sexual side effects. These men reported one or more of the following: less desire for sex; difficulty in achieving an erection; and, a decrease in the amount of semen. Each of these side effects occurred in less than 2% of men. These side effects went away in men who stopped taking PROPECIA. They also disappeared in most men who continued taking PROPECIA.

PROPECIA · (Finasteride) Tablets

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The active ingredient in PROPECIA is also used by older men at a five-times higher dose to treat enlargement of the prostate. Some of these men reported other side effects, including problems with ejaculation, breast swelling and/or tenderness and allergic reactions such as lip swelling and rash. In clinical studies with PROPECIA, these side effects occurred as often in men taking placebo as in those taking PROPECIA.

Tell your doctor promptly about these or any other unusual effects.

- I **PROPECIA can affect a blood test called PSA (Prostate-Specific Antigen) for the screening of prostate cancer. If you have a PSA test done, you should tell your doctor that you are taking PROPECIA.**

Storage and handling.

Keep PROPECIA in the original container and keep the container closed. Store it in a dry place at room temperature. **PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.**

Do not give your PROPECIA tablets to anyone else. It has been prescribed only for you. Keep PROPECIA and all medications out of the reach of children.

THIS LEAFLET PROVIDES A SUMMARY OF INFORMATION ABOUT PROPECIA. IF AFTER READING THIS LEAFLET YOU HAVE ANY QUESTIONS OR ARE NOT SURE ABOUT ANYTHING, ASK YOUR DOCTOR.

1-800-830-7375, Monday through Friday, 8:30 A.M. TO 7:00 P.M. (ET).

Issued December 1997

MERCK & CO., INC.
West Point, PA 19486, USA

Synopsis of Application

Finasteride 1 mg—5-Year Data
Synopsis of Application

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Overview

Finasteride 1 mg—5-Year Data
Synopsis of Application
A. Overview

A-1

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Synopsis of Application
A. Overview

A-2

LIST OF TABLES

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There are no tables in this document.

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A-3

LIST OF FIGURES

PAGE

There are no figures in this document.

Finasteride 1 mg—5-Year Data
Synopsis of Application
A. Overview

A-4

1. Organization

The Synopsis of Application is an overall summary of the application that documents the safety and efficacy of finasteride 1 mg (synonyms: PROPECIA¹, MK-0906, and L-652931) for the treatment of male pattern hair loss in men. The purpose of the Synopsis is to provide reviewers with an overview of the application and a good understanding of finasteride 1 mg.

The Synopsis of Application is organized as follows: after this Overview is the Proposed Text of Labeling, annotated with references to this synopsis and/or to the individual technical sections. The Labeling is followed by the remaining synopses: the Clinical Summary and the Commercial Marketing History. A list of references is included with each of the above Synopsis subsections.

2. Referencing

Within the various synopses, where appropriate, specific statements are referenced by bracketed alpha-numeric codes (e.g., [A-1]). These citations identify the individual supporting documents and cross-reference them to their actual locations within the technical sections of this application.

3. Quality Assurance

Data presented in this application were subject to audit by Merck Research Laboratories Quality Assurance organizations based on approved standard operating procedures in effect at the time of the audit. A Quality Assurance statement and a statement of compliance are included with each nonclinical safety study report. For clinical research studies, an audit information sheet is provided for each clinical study report documenting external and internal auditing activities and an assessment of compliance to Good Clinical Practice Standards for each protocol. Information presented in the label, synopsis, and each summary section has been audited against the supporting documentation provided herein in accordance with Merck Research Laboratories Worldwide Quality Assurance Resources Standard Operating Procedures.

The quality assurance audits meet the following U.S. and international regulations and guidelines: U.S. Food and Drug Administration Code of Federal Regulations (21 CFR Part 58), Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice (ISBN92-64-12367-9), and Rules Governing Medicinal Products in the European Community Guidelines III/3700/90/EN.

¹ PROPECIA is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

Proposed Text of Labeling

Finasteride 1 mg – 5 Year Data
Proposed Text of Labeling

B-1

1. Annotated Package Circular

This section contains the annotated package circular. For those annotations that have two references, the first reference is to the “Clinical Summary” subsection contained in this supplement in Item 8. The page number indicates the location of a brief description of the information supporting the labeling statement. The second reference is to the specific technical sections and gives the page numbers where a more detailed description of the supporting data can be found.

This section also contains the patient product information with proposed changes shown using revision marks.

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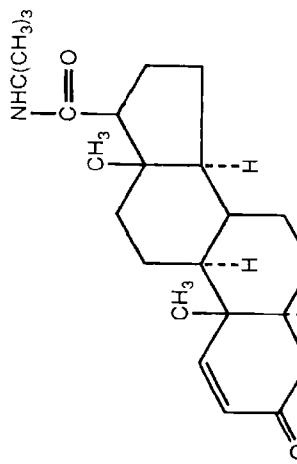
PROPECIA*

(Finasteride)
Tablets, 1 mg

DESCRIPTION

PROPECIA* (finasteride), a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5 α -reductase, an intracellular enzyme that converts the androgen testosterone into 5 α -dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-(5 α ,17 β)-. The empirical formula of finasteride is C₂₃H₃₆N₂O₂ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water.

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PROPECIA tablets for oral administration are film-coated tablets that contain 1 mg of finasteride and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, hydroxypropyl methylcellulose 2910, hydroxypropyl cellulose, titanium dioxide, talc, yellow ferric oxide, and red ferric oxide.

CLINICAL PHARMACOLOGY

Finasteride is a competitive and specific inhibitor of Type II 5 α -reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5 α -reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5 α -reductase is responsible for approximately one-third of circulating DHT. The Type II 5 α -reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5 α -reductase over Type I isozyme (IC_{50} =500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibition by finasteride is accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP $^+$. The turnover for the enzyme complex is slow ($t_{1/2}$ approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5 α -reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1-mg tablet.

In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. The relative contributions of these reductions to the treatment effect of finasteride have not

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PROPECIA® (Finasteride) Tablets, 1 mg

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been defined. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed. Finasteride had no effect on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, nor did it affect the plasma lipid profile (e.g., total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) or bone mineral density. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH) or follicle-stimulating hormone (FSH) were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone, indicating that the hypothalamic-pituitary-testicular axis was not affected. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

Pharmacokinetics

Following an oral dose of ¹⁴C-finasteride in man, a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces. The major compound isolated from urine was the monocarboxylic acid metabolite; virtually no unchanged drug was recovered. The t-butyl side chain monohydroxylated metabolite has been isolated from plasma. These metabolites possessed no more than 20% of the 5 α -reductase inhibitory activity of finasteride.

In a study in 15 healthy male subjects, the mean bioavailability of finasteride 1-mg tablets was 65% (range 26-170%), based on the ratio of AUC relative to a 5-mg intravenous dose infused over 60 minutes. Following intravenous infusion, mean plasma clearance was 165 mL/min (range, 70-279 mL/min) and mean steady-state volume of distribution was 76 liters (range, 44-96 liters). In a separate study, the bioavailability of finasteride was not affected by food.

Approximately 90% of circulating finasteride is bound to plasma proteins. Finasteride has been found to cross the blood-brain barrier.

There is a slow accumulation phase for finasteride after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9-13.7 ng/mL) and was reached 1 to 2 hours postdose; AUC_{0-24 hr} was 53 ng·hr/mL (range, 20-154 ng·hr/mL) and mean terminal half-life of elimination was 4.8 hours (range, 3.3-13.4 hours).

Semen levels have been measured in 35 men taking finasteride 1 mg daily for 6 weeks. In 60% (21 of 35) of the samples, finasteride levels were undetectable. The mean finasteride level was 0.26 ng/mL and the highest level measured was 1.52 ng/mL. Using this highest semen level measured and assuming 100% absorption from a 5-mL ejaculate per day,

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human exposure through vaginal absorption would be up to 7.6 ng per day, which is 750 times lower than the exposure from the no-effect dose for developmental abnormalities in Rhesus monkeys (see PRECAUTIONS, Pregnancy).

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age. These findings are of no clinical significance, and a reduction in dosage in the elderly is not warranted.

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment (creatinine clearance ranging from 9.0 to 55 mL/min), the values for AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ¹⁴C-finasteride were similar to those obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). Furthermore, finasteride has been well tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

Clinical Studies

The efficacy of PROPECIA was demonstrated in men (88% Caucasian) with mild to moderate androgenetic alopecia (male pattern hair loss) between 18 and 41 years of age. In order to prevent seborrheic dermatitis which might confound the assessment of hair growth in these studies,~~controlled phase and extensions~~, all men, whether treated with finasteride or placebo, were instructed to use a specified, medicated, tar-based shampoo (Neutrogena T/Gel®** Shampoo) during the first 2 years of the studies.¹

There were three double-blind, randomized, placebo-controlled studies of 12-month duration. The two primary endpoints were hair count and patient self-assessment; the two secondary endpoints were investigator assessment and ratings of photographs. The three studies were conducted in 1,879 men with mild to moderate, but not complete, hair loss. Two of the studies enrolled men with predominantly mild to moderate vertex hair loss (n=1,553). The third enrolled men having mild to moderate hair loss in the anterior mid-scalp area with or without vertex balding (n=326).

1. Sentence has been revised for clarity.
[Clinical Ref. P087C1: p. 36]

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Two studies on Vertex Baldness

Of the men who completed the first 12 months of the two vertex baldness trials, 1,215 elected to continue in double-blind, placebo-controlled, 12-month extension studies. There were 547 men receiving PROPECIA for both the initial study and first extension periods (up to 24 months, 2 years of treatment) and 60 men receiving placebo for the same periods.² The extension studies were continued for 3 additional years, with 323 men on PROPECIA and 23 on placebo entering the fifth year of the study.³

In order to evaluate the effect of discontinuation of therapy, ~~in addition~~, there were 65 men who received PROPECIA for the initial 12 months followed by placebo in the first 12-month extension period.⁴ Some of these men continued in additional extension studies and were switched back to treatment with PROPECIA, with 32 men entering the fifth year of the study.⁵ Lastly, there were ~~and~~ 543 men who received placebo for the initial 12 months followed by PROPECIA in the first 12-month extension period.⁶ Some of these men continued in additional extension studies receiving PROPECIA, with 290 men entering the fifth year of the study.⁷ (See ~~see~~ Figure below).

Hair counts were assessed by photographic enlargements of a representative area of active hair loss. In these two studies in men with vertex baldness, significant increases in hair count were demonstrated at 6 and 12 months in men treated with PROPECIA, while significant hair loss from baseline was demonstrated in those treated with placebo. At 12 months there was a 107-hair difference from placebo ($p<0.001$, PROPECIA [$n=679$ evaluable men] vs placebo [$n=672$ evaluable men]) within a 1-inch diameter circle (5.1 cm²). Hair count was maintained in those men taking PROPECIA (~~in 433 evaluable men~~) for up to 24 months.² While the placebo group (~~n=47 evaluable men~~) continued to show progressive hair loss, at 24 months, this resulted in a 138-hair difference between treatment groups ($p<0.001$, PROPECIA [$n=433$ evaluable men] vs placebo [$n=47$ evaluable men]) within the same area.⁹ In men treated with PROPECIA, the maximum improvement in hair count compared to baseline was achieved during the first 2 years, and hair count was maintained above baseline throughout the 5 years of the studies.¹⁰ The difference between treatment groups also continued to increase throughout the studies, resulting in a 277-hair difference ($p<0.001$, PROPECIA [$n=219$ evaluable men] vs placebo [$n=15$ evaluable men]) at 5 years.¹² Thus, compared to baseline, hair loss did not progress further in the majority of men treated with PROPECIA; in contrast, hair loss progressively worsened in all men in the placebo group (see Figure below).¹³

Patients who switched from placebo to PROPECIA ($n=426$ evaluable men) had ~~a~~ decrease in hair count at the end of the initial 12-months placebo period, followed by ~~had an~~

2. Sentence has been revised for clarity.
3. [Clinical Sum.: p. 9, 16]
[Clinical Ref. P087C1: p. 36, 67]
4. Sentence has been revised for clarity.
[Clinical Sum.: p. 8]
5. [Clinical Sum.: p. 9]
[Clinical Ref. P087C1: p. 36, 67]
6. Sentence has been revised for clarity.
7. [Clinical Sum.: p. 9]
[Clinical Ref. P087C1: p. 36, 67]
8. Revised for consistency of style throughout the circular
9. Sentence has been revised.
10. [Clinical Sum.: p. 11]
[Clinical Ref. P087C1: p. 81, 240]
11. [Clinical Sum.: p. 11]
[Clinical Ref. P087C1: p. 83, 240]
12. [Clinical Sum.: p. 6]
[Clinical Ref. P087C1: p. 83, 240]
13. [Clinical Sum.: p. 6, 15]
[Clinical Ref. P087C1: p. 81, 240]

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increase in hair count after ~~at 24 months~~¹ 1 year of treatment with PROPECIA. This increase in hair count was less (56 hairs above original baseline) than the increase (91 hairs above original baseline) observed after 1 year of treatment in men initially randomized to PROPECIA. Although the increase in hair count relative to when therapy was initiated, was comparable between these two groups, a higher absolute hair count was achieved in patients who were started on treatment with PROPECIA in the initial study. This advantage was maintained throughout the 5 years of the studies.¹⁴ A change of treatment from PROPECIA to placebo (n=48 evaluable men) at the end of the initial 12 months resulted in reversal of the increase in hair count 12 months later, at 24 months. (See Figure below) ~~for combined study results.~~

At 12 months, 58% of men in the placebo group ~~had 14%~~ of men treated with PROPECIA had further hair loss (defined as any decrease in hair count from baseline), compared with ~~58%~~ of men in the placebo group ~~14%~~ of men treated with PROPECIA. In men treated for up to 24 months 2 years, 72% of men in the placebo group ~~17%~~ of those treated with PROPECIA demonstrated hair loss, compared with ~~72%~~ of those in the placebo group ~~17%~~ of men treated with PROPECIA. At 5 years, 100% of men in the placebo group demonstrated hair loss, compared with 35% of men treated with PROPECIA.¹⁵

14. [Clinical Sum.: p. 11]
[Clinical Ref. P087C1: p. 81]
15. Revised for consistency of style throughout the circular.
16. Revised the sentence structure of the 12-month and 2-year data. Added 5-year data.
[Clinical Sum.: p.11]
[Clinical Ref. P087C1: p. 80]

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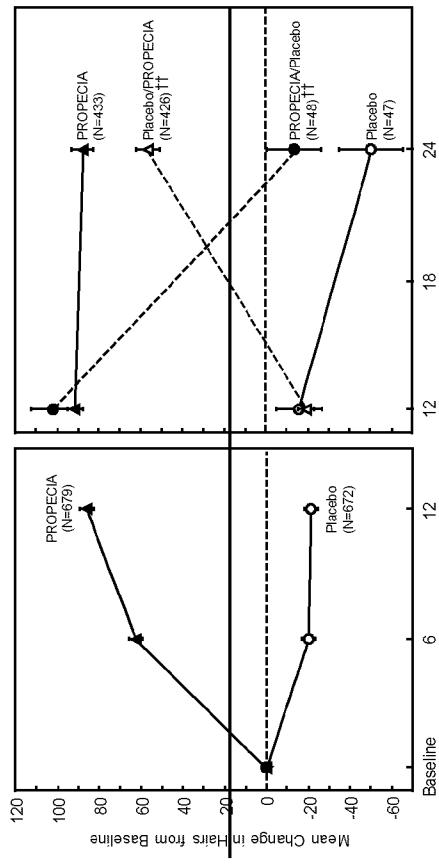
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Effect on Hair Count[†]

Number of Hairs in a 1-Inch Diameter Circle
Mean Change \pm 1 S.E.



[†] Pooled data from vertex hair loss studies (mean baseline hair count = 876).

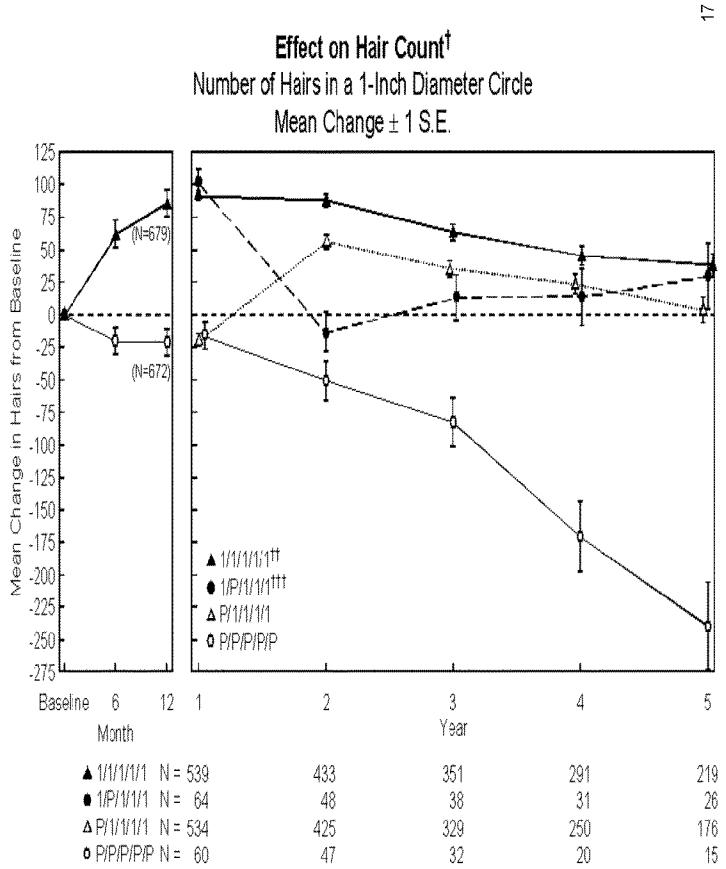
†† At the end of initial 12-month period, treatment switched from PROPECIA to placebo (----, PROPECIA/Placebo) or from placebo to PROPECIA (---, Placebo/PROPECIA).

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[†] Pooled data from vertex hair loss studies

†† 1 = finasteride, 1 mg

††† P = placebo

Patient self-assessment was obtained at each clinic visit from a self-administered questionnaire, which included questions on their perception of hair growth, hair loss, and appearance. This self-assessment demonstrated an increase in amount of hair, a decrease in hair loss, and improvement in appearance in men treated with PROPECIA. Overall improvement compared with placebo was seen as early as 3 months ($p<0.05$), with continued improvement over 24 months.⁵ Years.¹⁸ Investigator assessment was based on a 7-point scale evaluating increases or decreases in scalp hair at each patient visit. This assessment showed significantly greater increases in hair growth in men treated with PROPECIA compared with placebo as early as 3 months

17. Deleted interim graph containing data for up to 2 years of the studies. Added graph containing data for up to 5 years of the studies.
[Clinical Ref. P087C1: p. 81]

18. [Clinical Sum.: p.12]
[Clinical Ref. P087C1: p. 91]

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($p<0.001$). At 12 months, the investigators rated 65% of men treated with PROPECIA as having increased hair growth compared with 37% in the placebo group. At 24 months,²¹ years, the investigators rated 80% of men treated with PROPECIA as having increased hair growth compared with 47% of men treated with placebo. At 5 years, the investigators rated 77% of men treated with PROPECIA as having increased hair growth, compared with 15% of men treated with placebo.²⁰

An independent panel rated standardized photographs of the head were assessed in a blinded fashion based on increases or decreases in scalp hair, using ~~at the beginning of the study and at 6-, 12-, 18- and 24-months. An independent panel rated increases or decreases in scalp hair on the same 7-point scale as the investigator assessment.~~²¹ At 12 months, 48% of men treated with PROPECIA had an increase as compared with 7% of men treated with placebo. At 24 months²², an increase in hair growth was demonstrated in 66% of men treated with PROPECIA²³ compared with 7% of men treated with placebo. At 5 years, an increase in hair growth was demonstrated in 48% of men treated with PROPECIA, compared with 6% of men treated with placebo.²⁴ Based on this assessment, continued treatment with PROPECIA resulted in further improvement. These results were observed in the context of no further increase in hair count between month 12 and month 24. Based on this assessment, 10% of men treated with PROPECIA for 5 years were rated as having lost hair compared with 75% of men in the placebo group. These results demonstrate that 90% of the men treated with PROPECIA had no further visible progression of hair loss, compared with 25% of men treated with placebo, based on ratings of either no change or increased hair growth.²⁰

In one of the two vertex baldness studies, patients were questioned on non-scalp body hair growth. PROPECIA did not appear to affect non-scalp body hair.

Study on Hair Loss in the Anterior Mid-Scalp Area

A third study of 12-month duration, designed to assess the efficacy of PROPECIA in men with hair loss in the anterior mid-scalp area, also demonstrated significant increases in hair count compared with placebo. Increases in hair count were accompanied by improvements in patient self-assessment, investigator assessment, and ratings based on standardized photographs. Hair counts were obtained in the anterior mid-scalp area, and did not include the area of bitemporal recession or the anterior hairline.

Phototrichogram Study

A 48-week, placebo-controlled study designed to assess the effect of PROPECIA on the phases of the hair-growth cycle (growing phase, lagenal and resting phase, telogen) in vertex baldness enrolled 212 men with androgenetic alopecia.²⁰ At baseline and 48 weeks,

19. Revised for consistency of style throughout the circular.
[Clinical Sum.: p.12]
[Clinical Ref. P087C1: p. 150, 242]
20. [Clinical Sum.: p.12]
[Clinical Ref. P087C1: p. 150, 242]
21. Sentence revised for clarity.
22. Revised for consistency of style throughout the circular.
23. Editorial; added comma.
24. [Clinical Sum.: p.13]
[Clinical Ref. P087C1: p. 157, 243]
25. Deleted interim conclusion based on 2-year data.
[Clinical Sum.: p.13]
[Clinical Ref. P087C1: p. 157, 243]

26. [Clinical Sum.: p.13]
[Clinical Ref. P104C1: p. 22, 25, 158]

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total,²⁷ telogen,²⁸ and anagen²⁹ hair counts were obtained in a 1-cm² target area of the scalp.³⁰ Treatment with PROPECIA led to improvements in anagen hair counts, while men in the placebo group lost anagen hair.³⁰ At 48 weeks, men treated with PROPECIA showed net increases in total and anagen hair counts of 17 hairs (p<0.001),³² and 27 hairs (p<0.001),³² respectively, compared to placebo. This increase in anagen hair count, compared to total hair count, led to a net improvement in the anagen-to-telogen ratio of 47% (p<0.001) at 48 weeks for men treated with PROPECIA, compared to placebo.³⁴ These data provide direct evidence that treatment with PROPECIA promotes the conversion of hair follicles into the actively growing phase.³⁵

Summary of Clinical Studies

Clinical studies were conducted in men aged 18 to 41 with mild to moderate degrees of androgenetic alopecia. All men treated with PROPECIA or placebo received a tar-based shampoo (Neutrogena T/Gel®** Shampoo). During the first 2 years of the studies,³⁶ Clinical improvement was seen as early as 3 months in the patients treated with PROPECIA and led to a net increase in scalp hair count and hair regrowth. In addition, clinical studies for up to 5 years demonstrated treatment with PROPECIA prevented the further progression of hair loss observed in the placebo group.³⁷ In general, the difference between treatment groups continued to increase throughout the 5 years of the studies.³⁸ Slowing of hair loss with PROPECIA by patient self-assessment. These effects were maintained through the second year of treatment. Maintenance of improvement in clinical efficacy has also been demonstrated in controlled and open-extension studies for up to 3 years.³⁸

Ethnic Analysis of Clinical Data

In a combined analysis of the two studies on vertex baldness, mean hair count changes from baseline were 91 vs -19 hairs (PROPECIA vs placebo) among Caucasians (n=1,185), 49 vs -27 hairs among Blacks (n=84), 53 vs -38 hairs among Asians (n=17), 67 vs 5 hairs among Hispanics (n=45) and 67 vs -15 hairs among other ethnic groups (n=20). Patient self-assessment showed improvement across racial groups with PROPECIA treatment, except for satisfaction of the frontal hairline and vertex in Black men, who were satisfied overall. A sexual function questionnaire was self-administered by patients participating in the two vertex baldness trials to detect more subtle changes in sexual function. At Month 12, statistically significant differences in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems). However, no significant difference was seen in the question on overall satisfaction with sex life.

27. [Clinical Sum.: p. 13]
[Clinical Ref. P104C1: p. 65, 158]
28. [Clinical Sum.: p. 13]
[Clinical Ref. P104C1: p. 158]
29. [Clinical Sum.: p. 13]
[Clinical Ref. P104C1: p. 59, 158]
30. [Clinical Sum.: p. 13]
[Clinical Ref. P104C1: p. 35, 158]
31. [Clinical Ref. P104C1: p. 59-61, 159]
32. [Clinical Sum.: p. 13]
[Clinical Ref. P104C1: p. 66, 70]
33. [Clinical Sum.: p. 13]
[Clinical Ref. P104C1: p. 60, 64]
34. [Clinical Sum.: p. 14]
[Clinical Ref. P104C1: p. 159]
35. [Clinical Sum.: p. 7]
[Clinical Ref. P104C1: p. 160]
36. Sentence has been revised for clarity.
[Clinical Ref. P087C1: p. 36]
37. [Clinical Sum.: p. 15]
[Clinical Ref. P087C1: p. 80-81, 245]
38. [Clinical Sum.: p. 15]
[Clinical Ref. P087C1: p. 81, 92, 148, 155, 245]
39. Deleted interim 2-year conclusion and outdated information on maintenance of clinical efficacy.

CURRENT CIRCULAR SHOWING REVISIONS

COMMENTS/SUPPORT

PROPECIA · (Finasteride) Tablets, 1 mg

9328500

INDICATIONS AND USAGE

PROPECIA is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY**. Safety and efficacy were demonstrated in men between 18 to 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area (See CLINICAL PHARMACOLOGY, Clinical Studies).

Efficacy in bitemporal recession has not been established.

PROPECIA is not indicated in women (see CONTRAINDICATIONS).

PROPECIA is not indicated in children (see PRECAUTIONS, Pediatric Use).

CONTRAINDICATIONS

PROPECIA is contraindicated in the following:

Pregnancy. Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of 5 α -reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See also WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, Information for Patients and Pregnancy.) In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

Hypersensitivity to any component of this medication.

WARNINGS

PROPECIA is not indicated for use in pediatric patients (See INDICATIONS AND USAGE; and PRECAUTIONS, Pediatric Use) or women (see also PRECAUTIONS, Information for Patients and Pregnancy; and HOW SUPPLIED, Storage and Handling).

EXPOSURE OF WOMEN - RISK TO MALE FETUS

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (see also CONTRAINDICATIONS; PRECAUTIONS, Information for Patients and Pregnancy; and HOW SUPPLIED, Storage and Handling.)

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PROPECIA · (Finasteride) Tablets, 1 mg

PRECAUTIONS

General

Caution should be used in the administration of PROPECIA in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

Information for Patients

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also CONTRAINDICATIONS; WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; PRECAUTIONS, Pregnancy; and HOW SUPPLIED, Storage and Handling.)

See also Patient Package Insert.

Drug/Laboratory Test Interactions

In clinical studies with PROPECIA in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at Month 12. When finasteride is used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Until further information is gathered in men >41 years of age without BPH, consideration should be given to doubling the PSA level in men undergoing this test while taking PROPECIA.

Drug Interactions

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing enzyme system. Compounds that have been tested in man include antipyrine, digoxin, propranolol, theophylline, and warfarin and no interactions were found.

Other concomitant therapy: Although specific interaction studies were not performed, finasteride doses of 1 mg or more were concomitantly used in clinical studies with acetaminophen, α -blockers, analgesics, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H₂ antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolone anti-infectives without evidence of clinically significant adverse interactions.

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Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 888 and 2,192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated AUC_(0-24 hr) for animals and mean AUC_(0-24 hr) for man (0.05 µg·hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (1,824 times the human exposure). In mice at a dose of 25 mg/kg/day (184 times the human exposure, estimated), and in rats at a dose of ≥ 40 mg/kg/day (312 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (240 and 2,800 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (18.4 times the human exposure).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, when Chinese hamster ovary cells were treated with high concentrations (450-550 µmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 18,000-22,000 times the peak plasma levels in man given a total dose of 1 mg. Further, the concentrations (450-550 µmol) used in *in vitro* studies are not achievable in a biological system. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (1,824 times the human exposure, estimated) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4,344 times the estimated human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (488 times the estimated human exposure), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects

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PROPECIA · (Finasteride) Tablets, 1 mg

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were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats but is not relevant in man.

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS.
PROPECIA is not indicated for use in women.

Administration of finasteride to pregnant rats at doses ranging from 100 µg/kg/day to 100 mg/kg/day (5-5,000 times the recommended human dose of 1 mg/day) resulted in dose-dependent development of hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at ≥ 30 µg/kg/day (≥ 1.5 times the recommended human dose of 1 mg/day) and decreased anogenital distance when given finasteride at ≥ 3 µg/kg/day (one-fifth the recommended human dose of 1 mg/day). The critical period during which these effects can be induced in male rats has been defined to be days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5 α -reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5 α -reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 488 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (150 times the recommended human dose of 1 mg/day) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring. No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day (5000 times the recommended human dose of 1 mg/day). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of

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finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 100 times the recommended human dose of 1 mg/day or approximately 12 million times the highest estimated exposure to finasteride from semen of men taking 1 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

Nursing Mothers

PROPECIA is not indicated for use in women. It is not known whether finasteride is excreted in human milk.

Pediatric Use

PROPECIA is not indicated for use in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical efficacy studies with PROPECIA did not include subjects aged 65 and over. Based on pharmacokinetics, no dosage adjustment is necessary in the elderly (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

ADVERSE REACTIONS

Clinical Studies for PROPECIA (finasteride 1 mg) in the Treatment of Male Pattern Hair Loss

In controlled clinical trials for PROPECIA of 12-month duration, 1.4% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo); 1.2% of patients on PROPECIA and 0.9% of patients on placebo discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with PROPECIA or placebo, respectively: decreased libido (1.8%, 1.3%), erectile dysfunction (1.3%, 0.7%) and ejaculation disorder (1.2%, 0.7%; primarily decreased volume of ejaculate: [0.8%, 0.4%]). Integrated analysis of clinical adverse experiences showed that during treatment with PROPECIA, 36 (3.8%) of 945 men had reported one or more of these adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo ($p=0.04$). Resolution occurred in all men who discontinued therapy with PROPECIA due to these side effects and in 58% most

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of those who continued therapy. The incidence of each of the above side effects decreased to ≤ 0.3% by the fifth year of treatment with PROPECIA.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 mL (-11%) compared with 0.2 mL (-8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that finasteride at 5 times the dosage of PROPECIA (5 mg daily) produced significant median decreases of approximately 0.5 mL (-25%) compared to placebo in ejaculate volume but this was reversible after discontinuation of treatment.

In the clinical studies with PROPECIA, the incidences for breast tenderness and enlargement, hypersensitivity reactions, and testicular pain in finasteride-treated patients were not different from those in patients treated with placebo.

Postmarketing Experience for PROPECIA (finasteride 1 mg)

Breast tenderness and enlargement; hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face; and testicular pain.

Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR (finasteride 5 mg) in the Treatment of Benign Prostatic Hyperplasia*

In controlled clinical trials for PROSCAR of 12-month duration, 1.3% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (0.9% for placebo); only one patient on PROSCAR (0.2%) and one patient on placebo (0.2%) discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with PROSCAR or placebo, respectively: erectile dysfunction (3.7%, 1.1%), decreased libido (3.3%, 1.6%) and decreased volume of ejaculate (2.8%, 0.9%). The adverse experience profiles for patients treated with finasteride 1 mg/day for 12 months and those maintained on PROSCAR for 24 to 48 months were similar to that observed in the 12-month controlled studies with PROSCAR. Sexual adverse experiences resolved with continued treatment in over 60% of patients who reported them.

OVERDOSAGE

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions. Until further experience is obtained, no specific treatment for an overdose with finasteride can be recommended.

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Significant lethality was observed in male and female mice at single oral doses of 1,500 mg/m² (500 mg/kg) and in female and male rats at single oral doses of 2,360 mg/m² (400 mg/kg) and 5,900 mg/m² (1,000 mg/kg), respectively.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg once a day.
PROPECIA may be administered with or without meals.

In general, daily use for three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit. Withdrawal of treatment leads to reversal of effect within 12 months.

HOW SUPPLIED

No. 6642 — PROPECIA tablets, 1 mg, are tan, octagonal, film-coated convex tablets with “stylized P” logo on one side and PROPECIA on the other. They are supplied as follows:

NDC 0006-0071-31 unit of use bottles of 30

NDC 0006-0071-61 PROPAK®*** - carton of 3 unit of use bottles of 30.

Storage and Handling

Store at room temperature, 15-30°C (59-86°F). Keep container closed and protect from moisture.

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed. (See WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS, and PRECAUTIONS, Information for Patients and Pregnancy.)

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Dist. by:

MERCK & CO., INC., WhiteHouse Station, NJ 08889, USA⁴¹

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41. Editorial; deleted “Dist. by” from the Merck LOGO.

42. Editorial; deleted issue date.

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PROPECIA · (Finasteride) Tablets, 1 mg

932850Q

Issued May 2009⁴²
Printed in USA

932930Q

PROPECIA®* 
(Finasteride) Tablets
Patient Information about
PROPECIA · (Pro-pee-sha)
Generic name: finasteride
(fin-AS-tur-eyed)

PROPECIA is for use by MEN ONLY.**

Please read this leaflet before you start taking PROPECIA. Also, read the information included with PROPECIA each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss PROPECIA when you start taking your medication and at regular checkups.

What is PROPECIA used for?

PROPECIA is used for the treatment of male pattern hair loss on the vertex and the anterior mid-scalp area.

PROPECIA is for use by **MEN ONLY** and should **NOT** be used by women or children.

What is male pattern hair loss?

Male pattern hair loss is a common condition in which men experience thinning of the hair on the scalp. Often, this results in a receding hairline and/or balding on the top of the head. These changes typically begin gradually in men in their 20s.

Doctors believe male pattern hair loss is due to heredity and is dependent on hormonal effects. Doctors refer to this type of hair loss as androgenetic alopecia.

Results of clinical studies:

For 12 months, doctors studied over 1800 men aged 18 to 41 with mild to moderate amounts of ongoing hair loss. All men, whether receiving PROPECIA or placebo (a pill containing no medication) were given a medicated shampoo (Neutrogena T/Gel® *** Shampoo). Of these men, approximately 1200 with hair loss at the top of the head participated in additional extension studies, resulting in a total study time of up to five years. were studied for an additional 12 months. In general, men who took PROPECIA maintained or increased the number of visible scalp hairs and noticed improvement in their hair in the first year. Improvement, compared to the start of the study, continued throughout the five years of treatment, with the effect maintained in the second year. Hair counts in men who did not take PROPECIA continued to decrease.

In one study, patients were questioned on the growth of body hair. PROPECIA did not appear to affect hair in places other than the scalp.

Will PROPECIA work for me?

For most men, PROPECIA increases the number of scalp hairs, helping to fill in thin or balding areas of the scalp. Men taking PROPECIA noted a slowing of hair loss during two years of use. Although results

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PROPECIA · (Finasteride) Tablets

9329300

will vary, generally you will not be able to grow back all of the hair you have lost. There is not sufficient evidence that PROPECIA works in the treatment of receding hairline in the temporal area on both sides of the head.

Male pattern hair loss occurs gradually over time. On average, healthy hair grows only about half an inch each month. Therefore, it will take time to see any effect.

You may need to take PROPECIA daily for three months or more before you see a benefit from taking PROPECIA. PROPECIA can only work over the long term if you continue taking it. If the drug has not worked for you in twelve months, further treatment is unlikely to be of benefit. If you stop taking PROPECIA, you will likely lose the hair you have gained within 12 months of stopping treatment. You should discuss this with your doctor.

How should I take PROPECIA?

Follow your doctor's instructions.

- | Take one tablet by mouth each day.
- | You may take PROPECIA with or without food.
- | If you forget to take PROPECIA, do not take an extra tablet. Just take the next tablet as usual.

PROPECIA will not work faster or better if you take it more than once a day.

Who should NOT take PROPECIA?

- | PROPECIA is for the treatment of male pattern hair loss in **MEN ONLY** and should not be taken by women or children.
- | Anyone allergic to any of the ingredients.

A warning about PROPECIA and pregnancy.

- | **Women who are or may potentially be pregnant:**
 - **must not use PROPECIA**
 - **should not handle crushed or broken tablets of PROPECIA.**

If a woman who is pregnant with a male baby absorbs the active ingredient in PROPECIA, either by swallowing or through the skin, it may cause abnormalities of a male baby's sex organs. If a woman who is pregnant comes into contact with the active ingredient in PROPECIA, a doctor should be consulted. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

What are the possible side effects of PROPECIA?

Like all prescription products, PROPECIA may cause side effects. In clinical studies, side effects from PROPECIA were uncommon and did not affect most men. A small number of men experienced certain sexual side effects. These men reported one or more of the following: less desire for sex; difficulty in achieving an erection; and, a decrease in the amount of semen. Each of these side effects occurred in less than 2% of men. These side effects went away in men who stopped taking PROPECIA. They also disappeared in most men who continued taking PROPECIA.

PROPECIA · (Finasteride) Tablets

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In general use, the following have been reported infrequently: allergic reactions including rash, itching, hives and swelling of the lips and face; problems with ejaculation; breast tenderness and enlargement; and testicular pain.

Tell your doctor promptly about these or any other unusual side effects.

- I **PROPECIA can affect a blood test called PSA (Prostate-Specific Antigen) for the screening of prostate cancer. If you have a PSA test done, you should tell your doctor that you are taking PROPECIA.**

Storage and handling.

Keep PROPECIA in the original container and keep the container closed. Store it in a dry place at room temperature. **PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.**

Do not give your PROPECIA tablets to anyone else. It has been prescribed only for you. Keep PROPECIA and all medications out of the reach of children.

THIS LEAFLET PROVIDES A SUMMARY OF INFORMATION ABOUT PROPECIA. IF AFTER READING THIS LEAFLET YOU HAVE ANY QUESTIONS OR ARE NOT SURE ABOUT ANYTHING, ASK YOUR DOCTOR.

1-888-637-2522, Monday through Friday, 8:30 A.M. TO 7:00 P.M. (ET).

www.propecia.com

Issued May 2000

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

Clinical Summary

*This Clinical Summary is reproduced exactly as it appears in the
Clinical and Statistical Documentation Section, Item 8*

Finasteride 1 mg—5-Year Data
Clinical Summary

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1. Introduction

This Supplemental New Drug Application (sNDA) is submitted to support the update to the U.S. Package Circular (USPC) for PROPECIATM¹ (finasteride 1 mg) based on long-term data from the Phase III double-blind extension studies (Protocols 087 and 089) and data from the Phototrichogram Study (Protocols 104 and 106). These studies were undertaken to assess the effect of finasteride on the phases of the hair growth cycle in men with male pattern hair loss. In addition, there are data from the open extensions to Phase II Pilot (Protocol 047) and Dose-Range (Protocol 081) studies.

The Clinical Summary briefly reviews the 5-year efficacy and safety data from the Phase III Pivotal studies. Over the 5-year study period (including the original 12-month, double-blind, placebo-controlled study and subsequent placebo-controlled extensions), treatment with finasteride has been shown to increase hair growth, compared with baseline and placebo, as well as to slow progression of further hair loss. Data from the 5-year and 6-year open-label extensions of 2 Phase II clinical studies are also reviewed here. Lastly, the Phototrichogram Study, reported in this sNDA, has suggested that the beneficial effect of finasteride on hair growth is mediated by an increase in the number of actively growing hairs (anagen phase) and improvement in the ratio of growing-to-resting (telogen phase) hairs. Data from the Phase II and III extension studies have demonstrated, furthermore, a favorable safety profile over long-term treatment.

The revised USPC, also included in this sNDA, adds the 5-year efficacy data on hair count for both finasteride- and placebo-treated groups (based on hair count, patient self-assessment, investigator assessments, and global photography assessments by an expert panel of dermatologists in the extensions to the Phase III Pivotal trials); results of the Phototrichogram Study, evaluating the effect of finasteride on the phases of the hair growth cycle in men with male pattern hair loss; a new graph containing hair count data from Years 1 through 5; and an updated safety profile based on 5-year data.

2. Overview

Male pattern hair loss (androgenetic alopecia) is a genetically determined disorder that affects a large proportion of adult men. This disorder is characterized by progressive miniaturization of hair follicles and loss of cosmetically important terminal hair in the vertex, mid, and frontal regions of the scalp. Androgens are necessary for the expression of male pattern hair loss [9]. Dependence on the specific androgen dihydrotestosterone (DHT) was suggested by the fact that men with genetic deficiency of the steroid α

α DHT and do not develop male pattern hair loss [10].

$\alpha!$

DHT, resulting in significant decreases in serum and tissue DHT levels [11]. The hypothesis that finasteride might have utility in the treatment of men with male pattern

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hair loss was further supported by the findings that finasteride reduced scalp DHT in balding men [12] and promoted hair growth in an animal model of male pattern hair loss, the Stumptail Macaque [13].

Based on these findings, together with the extensive safety data from long-term clinical studies and the marketed use of finasteride (5 mg) in over one million men with benign prostatic hyperplasia (BPH), Merck Research Laboratories conducted a clinical development program to evaluate the efficacy and safety of finasteride in men with male pattern hair loss.

The Phase II Pilot and Dose-Range studies (Protocols 047 and 081) established the clinical efficacy of finasteride in the treatment of men with male pattern hair loss and identified finasteride 1 mg as the appropriate dose for further investigation in the Phase III studies [1; 2; 3; 4].

The Phase III studies consisted of three 1-year, double-blind, placebo-controlled studies with finasteride 1 mg. Two of the studies were conducted in men with predominantly vertex hair loss, 1 in the United States (Protocol 087, N=933) and 1 in 15 other countries (Protocol 089, N=620) and referred to as the "U.S. Pivotal" and "International Pivotal" studies, respectively, or collectively as the "Pivotal" studies. The third study, referred to as the "Frontal Hair Loss" study (Protocol 092, N=326), enrolled men with predominantly frontal hair loss. The objective of these Phase III studies was to establish the safety and efficacy profile of finasteride in randomized, double-blind, placebo-controlled studies in men with male pattern hair loss. Efficacy was evaluated by a comprehensive set of endpoints: hair count, patient self-assessment, investigator assessment, and global photographic assessment. Data from the three 1-year, Phase III studies demonstrated that treatment with finasteride 1 mg/day produced statistically and clinically significant improvements in hair growth in the vertex and frontal regions of the scalp, compared with baseline and placebo, based on all 4 efficacy measures. The tolerability of finasteride 1 mg in these studies was excellent. The only drug-related clinical adverse experiences that were reported with an incidence $\geq 1\%$ of patients were decreased libido (1.8% versus 1.3% for placebo), erectile dysfunction (1.3% versus 0.7% for placebo), and ejaculation disorder (1.2% versus 0.7% for placebo). The incidence of laboratory adverse experiences was low and similar for the 2 treatment groups (finasteride, 6.7%; placebo, 6.1%). Twenty-three patients (2.6%) in the finasteride group and 21 patients (2.4%) in the placebo group had laboratory adverse experiences considered by the investigator to be drug related. The low rate of laboratory adverse experiences reported in patients treated with finasteride is consistent not only with its specific mechanism of action, but also with the previous experience with finasteride 5 mg in the treatment of BPH [5; 6; 7].

The design of the Phase III Pivotal studies (Protocols 087 and 089) included 1-year, double-blind, placebo-controlled extensions, during which a small percentage of the original finasteride group was switched to placebo and a large percentage of the original placebo group was switched to finasteride. Data from these blinded extension studies

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demonstrated maintenance or improvement in efficacy by all efficacy measures for patients treated with finasteride for 2 years, compared to results obtained at 1 year. Patients treated with placebo for 2 years continued to lose hair. These findings, together with the data from the open extensions to the Phase II Pilot and Dose-Range studies (up to 3 years of observation), comprised the core clinical efficacy and safety data submitted to support the original marketing application, and these data appear in the approved physician's circular for PROPECIA.

The Phase III Pivotal studies were extended for a further 3 years (three 1-year, double-blind, placebo-controlled extensions), thus, providing 5 years of placebo-controlled observations and enabling collection of longer-term efficacy and safety information. The open extensions to the Phase II studies (Protocols 047 and 081) were also extended on an annual basis for up to 6 years and 5 years of observation, respectively. An additional efficacy study, the Phototrichogram Study (Protocols 104 and 106), was undertaken to assess the effect of finasteride on the phases of the hair growth cycle in men with male pattern hair loss.

The placebo-controlled extensions to the Phase III Pivotal studies allowed the efficacy of finasteride to be assessed in the context of the natural progression of untreated hair loss. The data from these extension studies represent the longest placebo-controlled observations in men with male pattern hair loss. The results over the 5-year study period support a sustained benefit in hair growth for men receiving finasteride 1 mg, compared with baseline or placebo. Conversely, data from the placebo group documented the progressive deterioration in scalp hair in untreated men with male pattern hair loss over 5 years. At the end of the studies (Year 5), 65% of finasteride-treated men (N=219) had gained hair as assessed by hair count, while all of the men treated with placebo (N=15) had lost hair. Consistent with the hair count data, 60% of finasteride-treated men reported their bald spot getting smaller, compared with 20% of placebo-treated men; and 90% of finasteride-treated patients reported beneficial effects on the slowing of hair loss, compared with 66% of placebo-treated men. Overall satisfaction with the appearance of scalp hair was positively reported by 63% of finasteride-treated men, compared with 20% of placebo-treated men. Both the investigator assessment and the global photographic assessment demonstrated that, during the 5 years of observation, finasteride-treated men maintained or improved their hair growth, compared with placebo-treated men. At the end of the studies, 90% of finasteride-treated men demonstrated no change (42%) or improvement (48%) in hair growth by global photographic assessment, compared with 25% of placebo-treated patients (19% no change; 6% improvement), while 75% of placebo-treated men were rated as having lost hair, compared with 10% of finasteride-treated men. Safety data from 5 years of controlled observation in the Phase III studies provide reassurance that long-term use of finasteride 1 mg in men with male pattern hair loss is generally well tolerated and not associated with any new safety concerns. The incidence of drug-related sexual adverse experiences declined during the course of the extension studies to ≤0.3% for any of the side effects reported in the first year [P087C1].

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Additional long-term data from the open extensions to the Phase II Pilot study (Protocol 047) and the Phase II Dose-Range study (Protocol 081) demonstrated that mean hair count was maintained, compared with baseline, in men treated with finasteride for up to 6 years. In addition, hair growth was improved, compared with baseline, based on patient self-assessment, investigator assessment, and global photographic assessment in men treated with finasteride for up to 6 years. Safety data from these open extension studies confirmed the safety profile of finasteride and provided no evidence of an increase in the incidence of drug-related adverse experiences or identification of new adverse experiences associated with long-term treatment [P047X1; P081X1].

The efficacy of finasteride in the treatment of men with male pattern hair loss is further supported by data from the Phototrichogram Study (Protocols 104 and 106). This study demonstrated that treatment with finasteride favorably affects the hair growth cycle by promoting hair follicles into the anagen phase and increasing the anagen-to-telogen ratio. At the end of the 48-week study, finasteride-treated men had a mean increase in anagen hair count of 27 hairs (26%) and a mean increase in the anagen-to-telogen ratio of 47%, compared with men treated with placebo [P104C1].

In the aggregate, the data presented in this submission indicate that treatment with finasteride favorably affects the hair growth cycle, stabilizes hair loss over 5 years, and leads to a progressive increase in the treatment effect of finasteride (expressed as the difference from placebo) on scalp hair growth in men with male pattern hair loss. In addition, finasteride has an excellent safety profile and is generally well tolerated; there is no evidence of an increase in the incidence of drug-related adverse experiences or other new safety concerns with long-term treatment with finasteride.

3. Efficacy

3.1 The Phase III Pivotal Studies

The 2 Phase III Pivotal studies (Protocols 087 and 089) were undertaken to investigate the safety and efficacy of finasteride 1 mg in the treatment of men with male pattern hair loss. To support the hypothesis that treatment with finasteride slows the progression of further hair loss, an additional objective of these 2 studies was the demonstration of hair loss in the placebo group. These studies enrolled 1553 men with mild-to-moderate but not severe vertex hair loss (modified Norwood Hamilton II vertex, III vertex, IV, and V). Eligible patients were randomized to treatment with finasteride 1 mg or placebo [3; 4].

3.1.1 Study Design

The 2 Phase III Pivotal studies were designed as double-blind, placebo-controlled, 1-year studies (1:1 randomization to finasteride 1 mg or placebo; N=1553), followed by double-blind, placebo-controlled, 1-year extension studies. Men who entered the 1-year extension studies (Protocols 087-10 and 089-10) received treatment in the second year based on assignment made at initial randomization. A small percentage of the original finasteride group was blindly switched to placebo and a large percentage of the original

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placebo group was blindly switched to finasteride. Thus, 90% of men were randomized to finasteride 1 mg and 10% to placebo (Figure 1). These extension studies allowed blinded assessment of the effect of finasteride over 2 years of treatment; the effect of withdrawal of therapy (patients switched from finasteride to placebo); the effect of initiating treatment in men with documented hair loss (patients switched from placebo to finasteride); and the natural history of male pattern hair loss in men seeking treatment (patients remaining on placebo).

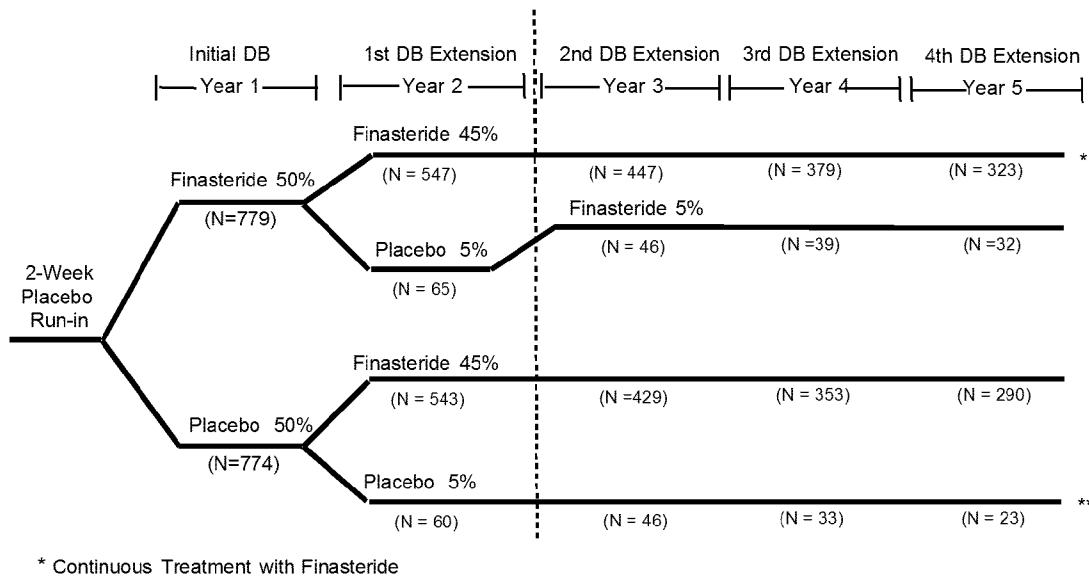
Men completing the first controlled extensions to the Phase III Pivotal studies at the end of 2 years were eligible to enroll in the second controlled extension studies (third year, Protocols 087-20 and 089-20; N=968). In these second extension studies, 95% of men received finasteride and 5% received placebo. Similarly, upon completing these second extension studies, men were eligible to enroll in the third controlled extension studies (fourth year, Protocols 087-30 and 089-30; N=804), and upon completing these third extension studies, men were eligible to enter the fourth (and last) controlled extension studies (fifth year, Protocols 087-40 and 089-40; N=668). Unlike the design of the first and second controlled extension studies (Years 2 and 3), all men who enrolled in the third and fourth extension studies (Years 4 and 5) remained on the therapy to which they had been assigned in the second extension studies (Year 3). The treatment assignments over the 5 years of controlled observation are presented in Figure 1. This report focuses on the 2 groups which received either finasteride 1 mg or placebo continuously for 5 years.

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Figure 1

Treatment Assignments in Each Year of the Phase III Pivotal Studies



DB = Double blind.
[5; 6; P087C1]

3.1.2 Objectives

The primary objectives of the Phase III Pivotal studies were to assess the efficacy and safety of finasteride in the treatment of men with male pattern hair loss. The double-blind, placebo-controlled extensions to the Phase III Pivotal studies were undertaken to: (1) determine whether treatment with oral finasteride 1 mg /day increases scalp hair in men with male pattern hair loss, compared to treatment with placebo; and (2) evaluate the safety and tolerability of oral finasteride in patients with male pattern hair loss. Efficacy was evaluated by a comprehensive set of 4 predefined endpoints: hair count, patient self-assessment, investigator clinical assessment, and global photographic assessment. Each endpoint is a separate measure of a different but related aspect of efficacy. Hair count provides a quantitative measure of treatment efficacy in a local, representative, 1-inch diameter (5.1 cm^2) area of active hair loss in the balding scalp. Patient self-assessment using a validated hair growth questionnaire enables patients to report their perception of hair growth or loss and their satisfaction with the appearance of their hair. Investigator assessment provides a measure from the treating physician's

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perspective of patient improvement in the clinic. Global photographic assessment of pretreatment and posttreatment photographs by an expert panel of dermatologists provides an objective and clinically relevant visual assessment of treatment efficacy.

3.1.3 Two-Year Results

As described in the approved label for PROPECIA™, data on finasteride-treated patients from each of the 2 Phase III Pivotal studies demonstrated comparable improvements both from baseline and compared with placebo in hair counts in a representative 5.1 cm² area of scalp hair. In a combined analysis of the 2 studies, there was an increase of 107 hairs (14%) after 1 year and 138 hairs (16%) after 2 years of treatment with finasteride, compared to treatment with placebo. At 1 year, only 14% of men treated with finasteride demonstrated hair loss (based on decrease in hair count from baseline), compared with 58% of men treated with placebo. At 2 years, only 17% of men treated with finasteride demonstrated hair loss, compared with 72% of men treated with placebo. The quantitative improvements measured by scalp hair count with finasteride were supported by the results of the patient self-assessment, investigator assessment, and global photographic assessment. Most men treated with finasteride for 2 years reported significant increases in hair growth, slowing of hair loss, and improvement in appearance of hair, compared to men treated with placebo. At 1 year, 65% of men treated with finasteride were rated as improved based on investigator assessment, compared with 37% of men treated with placebo; at 2 years, 80% of men treated with finasteride were rated as improved, compared with 47% of men treated with placebo. Similarly, the expert panel of dermatologists assessing global photographs rated 48% of men treated with finasteride as improved at 1 year, compared with 7% of men treated with placebo; and at 2 years, 66% of men treated with finasteride were rated as improved, compared with 7% of men treated with placebo.

As part of Protocols 087-10 and 089-10 described above, a small percentage (10%) of the original finasteride group was blindly switched to placebo after the first year and a large percentage (90%) of the original placebo group was blindly switched to finasteride (see Figure 1). Men who were switched from placebo to finasteride had a decrease in hair count at the end of the initial 12 months, followed by an increase in hair count after 1 year of treatment with finasteride. In contrast, the change of treatment from finasteride to placebo at the end of the initial 12 months resulted in a reversal of the increase in hair count at 24 months.

3.1.4 Five-Year Results

The efficacy results over the 5-year period of observation demonstrate continued benefits in hair growth by all predefined endpoints (hair counts, patient self-assessment, investigator assessment, and global photographic assessment) for men treated with finasteride 1 mg, compared both with baseline and with men receiving placebo [P087C1].

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3.1.4.1 Hair Count

Hair counts from a predefined, representative 5.1 cm² area of the scalp with active hair loss demonstrated an increase from baseline of 38 hairs for men treated with finasteride for 60 months, while men treated with placebo for 60 months demonstrated a decrease from baseline of 239 hairs. The difference between treatment groups was 277 hairs (p<0.001). While the increase from baseline hair count at Months 36, 48, and 60 was less than that observed at Month 24 for men treated with finasteride, for men treated with placebo there was further decline in hair count between Month 24 and all subsequent time points. Thus, for men treated with finasteride for 60 months, the net treatment effect (finasteride-placebo) increased from 138 hairs at Month 24 to 146 hairs at Month 36; 216 hairs at Month 48; and 277 hairs at Month 60. At Month 60, 65% of finasteride-treated patients had gained hair based on hair count, while all men (N=15) treated with placebo had lost hair.

Men who were switched from placebo to finasteride, as part of Protocols 087-10 and 089-10 described above (see Figure 1), had a decrease in hair count at the end of the initial 12-month placebo period, followed by an increase in hair count after 1 year of treatment with finasteride. This increase in hair count was less (56 hairs above original baseline) than the increase (91 hairs above original baseline) observed after 1 year of treatment in men initially randomized to finasteride. Although the increase in hair count, relative to when therapy with finasteride was initiated, was comparable in both groups, a higher absolute hair count was achieved in patients who were started on treatment with finasteride in the initial study. This advantage in absolute hair count was maintained throughout the 5 years of the studies.

3.1.4.2 Patient Self-Assessment

While hair count data provide important information about a local, representative area of scalp hair loss, the validated patient self-assessment questionnaire provides a mechanism for the patient to judge the benefits of treatment under controlled and blinded conditions. The questionnaire asked specific questions about the patient's scalp hair growth or loss and his satisfaction with the appearance of his hair. Data from the patient hair growth questionnaire consistently demonstrated that men treated with finasteride for 60 months had a more positive self-assessment of their scalp hair growth than men treated with placebo. For example, at Month 60, there were significant improvements from baseline for finasteride-treated patients for all 7 questions of the questionnaire, whereas for placebo-treated patients, there were declines from baseline for 5 of the 7 questions. Furthermore, finasteride-treated patients in general demonstrated greater improvement in hair growth at Month 60 than at Month 24, based on this questionnaire. Although this greater improvement could be due in part to a self-selected patient population in the extension studies, it should be noted that the patients on placebo were also self-selected. Any bias, therefore, would be expected to be observed in both treatment groups. However, a greater net treatment effect at 60 months (finasteride-placebo) remains consistent with that based on hair counts, which showed a further separation between the

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2 treatment groups over time. At Month 60, 60% of finasteride-treated patients reported their bald spot getting smaller, compared with only 20% of placebo-treated patients, and 90% of finasteride-treated patients reported beneficial effects on slowing hair loss, compared with 66% of placebo-treated patients. Overall satisfaction with the appearance of scalp hair was reported by 63% of finasteride-treated patients, compared with only 20% of placebo-treated patients. Consistent with other patient questionnaires, patient self-assessment in these studies had a greater placebo effect than the more objective assessments of hair count and global photographic assessment. Despite this placebo effect, the superiority of finasteride treatment over placebo in increasing hair density and stabilizing hair loss in men treated with finasteride for 60 months was demonstrated by the patient self-assessment questionnaire used in these studies.

3.1.4.3 Investigator Assessment

Assessment of the patient by the treating physician provides a clinically relevant assessment of the patient's hair growth or loss from baseline. The investigator was asked to respond to the following question using a 7-point scale: "As the investigator, how would you subjectively rate the patient's hair at this time point compared to baseline?"

At Month 60, the mean scores for the investigators' assessments were 1.4 and -0.6 for the finasteride and placebo groups, respectively, demonstrating significantly greater efficacy for the finasteride group over the placebo group ($p<0.001$). Although there was essentially no change in the investigator assessment between Month 24 and Month 60 for finasteride-treated patients, there was a significant decrease for placebo-treated patients during the same time period. Thus, the net treatment effect as assessed by the investigators increased between Month 24 and Month 60, indicating further separation between the treatment groups over time. At Month 60, 93% of finasteride-treated patients demonstrated maintenance (15%) or improvement (77%) in hair growth, compared with 62% of placebo-treated patients (46% maintenance; 15% improvement). As with the patient self-assessment, this endpoint had a greater placebo effect than the more objective endpoints of hair counts and global photographic assessment. Such an effect is not unusual in double-blind, placebo-controlled studies, and is often due to an expectation bias on the part of the patient's treating physician. Although patients treated with placebo for 60 months clearly lost hair (mean change of 239 hairs in a representative 5.1 cm^2 area), the investigator rated only 38% as having lost hair, with the remainder (62%) of these patients as having maintained or improved their hair growth. Nevertheless, as with the patient self-assessment, the beneficial effect of finasteride was demonstrated, in spite of the placebo rate, by the standardized assessments made by the investigators in these studies.

3.1.4.4 Global Photographic Assessment

Global photographic assessment of standardized clinical photographs by an independent expert panel of dermatologists blinded to treatment provides a highly objective overall assessment of treatment efficacy based primarily on scalp coverage. Each dermatologist

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independently evaluated paired global photographs (baseline and posttreatment) for each patient under identical lighting conditions and image size. Ratings were based on the same standardized 7-point scale as used for the investigator assessment.

At Month 60, the mean scores for the global photographic assessment were 0.6 and -1.4 for the finasteride and placebo groups, respectively, demonstrating significantly greater efficacy for the finasteride group over the placebo group ($p<0.001$). At Month 60, 90% of finasteride-treated patients demonstrated maintenance (42%) or improvement (48%) in hair growth, compared with 25% of placebo-treated patients (19% maintenance; 6% improvement). Conversely, 75% of placebo-treated patients were rated as having lost hair, compared with only 10% of finasteride-treated patients. These assessments by the expert panel of dermatologists substantiate the loss of hair in the placebo group, quantified by hair count, and confirm the efficacy of finasteride in stabilizing hair loss in 90% of men treated with finasteride for 60 months.

3.2 Phototrichogram Study

An additional efficacy study, the Phototrichogram Study (Protocols 104 and 106), was undertaken to assess the effect of finasteride on the phases of the hair growth cycle in men with male pattern hair loss [P104C1].

In the Phase III studies with finasteride, efficacy was assessed by changes in hair counts obtained from macrophotographs taken in a defined area of the scalp. This methodology counted “total” hair (anagen and telogen) and provided a static perspective of an otherwise dynamic process of hair growth, stasis, and loss, and did not differentiate hairs which were actively growing (in the anagen phase) from those which were resting and nongrowing (in the telogen phase). The phototrichogram method of quantifying hair growth is a noninvasive technique which provides reproducible assessments of the number of hair follicles in the anagen phase relative to the total hair count, and thereby allows dynamic measurements of the hair growth cycle. On the basis of macrophotographs taken a few days apart of a defined region of clipped scalp hair, hairs in anagen phase, which have a growth rate of about 0.35 mm/day, can be differentiated from resting, nongrowing, telogen-phase hairs.

3.2.1 Study Design

Two hundred twelve men, ages 18 to 40 years, with androgenetic alopecia predominately at the vertex scalp were randomized to receive finasteride 1 mg or placebo for 48 weeks. Total and anagen hair counts were obtained from macrophotographs of clipped hair in a defined 1 cm^2 target area of the scalp. Telogen hair count was defined as the numerical difference between total and anagen hair counts.

3.2.2 Results

At Week 48, finasteride-treated men had a mean increase from baseline in total and anagen hair counts of 17.3 hairs (8.3%) and 27 hairs (26%), respectively, compared with men treated with placebo ($p<0.001$ for both comparisons). Furthermore, treatment with

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finasteride resulted in a mean increase from baseline of 47% in the anagen-to-telogen ratio at 48 weeks, compared with placebo ($p<0.001$). As with the Phase III studies, treatment with finasteride for 48 weeks resulted in improvement in hair growth based on global photographic assessment, investigator assessment, and patient self-assessment, compared with treatment with placebo.

3.3 Phase II Open Extension Studies

The Phase II Pilot study (Protocol 047) was undertaken to determine the efficacy of finasteride 5 mg in the treatment of men with male pattern hair loss. Patients entering the study were randomized to receive finasteride 5 mg or placebo daily for 12 months [1]. Patients completing the initial 12-month, placebo-controlled study were eligible to enroll in the first open extension study, with all patients receiving finasteride 5 mg/day for the first 6 months [2]. Results from a separate study (Protocol 065) demonstrated that treatment with finasteride 5 mg/day and 1 mg/day for 6 weeks suppressed both scalp and serum DHT to a similar degree [8]. Therefore, all patients enrolled in the first open extension study were switched from finasteride 5 mg/day to finasteride 1 mg/day at Month 18. As patients completed each extension study, they were eligible to enroll in the next 12-month, open extension study up to the fifth (and last) extension study (Months 61 to 72) [P047X1].

The Phase II Dose-Range study (Protocol 081) was undertaken to determine the optimal dose of finasteride for further clinical investigation in the treatment of men with male pattern hair loss. Patients entering the study were randomly assigned to either finasteride 1, 0.2, or 0.01 mg or to placebo daily for 6 months [3]. All patients who completed the initial 6-month, placebo-controlled study were eligible for participation in a 6-month, double-blind extension study without placebo. In this double-blind extension study, patients who had received finasteride during the initial placebo-controlled study continued on the same dose of finasteride. Patients who had been randomized to placebo in the initial study were rerandomized to 1 of the 3 finasteride dosage groups [4]. At the end of the double-blind extension study (Month 12), every patient who had completed the study was given the opportunity to enroll in a 12-month, open extension study in which all patients were treated with finasteride 1 mg/day. As patients completed each open extension study they were given the opportunity to enroll in the next extension study, up to the fifth and last extension (fourth open extension, Months 49 to 60) [P081X1].

Long-term (6-year and 5-year) data from these open extensions to the Phase II Pilot (Protocol 047) and Dose-Range (Protocol 081) studies, demonstrated that hair count was maintained, compared to baseline, for up to 6 years. Cosmetic improvements in hair growth based on patient self-assessment, investigator assessment, and global photographic assessment were also observed in men who remained in these open extension studies for up to 6 years [P047X1; P081X1].

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3.4 Overall Efficacy Conclusions (Phase II/III Studies)

1. Treatment with finasteride 1 mg/day for 60 months stabilizes hair loss and/or increased hair growth in men with male pattern hair loss, based on hair counts and evaluations by the patient, the investigator, and an independent panel of dermatologists rating standardized clinical photographs.
2. Treatment with placebo for 60 months results in progressive deterioration in scalp hair growth in men with male pattern hair loss.
3. In general, the net treatment effect of finasteride 1 mg/day, compared with placebo, increases with continued use over 60 months in men with male pattern hair loss.
4. Treatment with finasteride 1 mg/day for 48 weeks favorably affects the hair growth cycle by promoting hair follicles into the anagen phase.

4. Safety

In the original marketing application, the safety of finasteride for the treatment of men with male pattern hair loss was evaluated in 3217 men participating in clinical trials. Additionally, extensive safety data exist from clinical trials and marketed experience with finasteride 5 mg for the treatment of men with BPH. Consistent with the experience with finasteride 5 mg, a low incidence of adverse events was observed in the clinical studies with finasteride 1 mg in the treatment of men with male pattern hair loss. Potential pharmacological effects of finasteride 1 mg were also examined, and the results were reassuring, corroborating the excellent safety and tolerability profile of the drug in this patient population. The 3 Phase III placebo-controlled studies (U.S. and International Pivotal and Frontal Hair Loss studies) provided an opportunity to assess the safety profile of finasteride 1 mg/day in a large population (finasteride 1 mg = 945, placebo = 934).

4.1 Two-Year Results

In the first year of the Phase III studies, the overall incidence of drug-related adverse experiences was similar across treatment groups: 7.7% in the finasteride group and 7% in the placebo group. Only 13 (1.4%) out of 945 patients in the finasteride group and 15 (1.6%) out of 934 patients in the placebo group were discontinued due to a drug-related clinical adverse experience. Overall, the number of clinical adverse experiences was low and balanced between treatment groups, except for a greater number of drug-related sexual adverse experiences in the finasteride group (3.8% versus 2.1%, p=0.041). The adverse experience profile of the 547 patients in the finasteride group who continued in the first extension study (up to 2 years) was similar to that observed in Year 1.

4.2 Five-Year Results

The controlled safety data on patients treated continuously with finasteride 1 mg or placebo in the extensions to the Phase III Pivotal studies are presented in this supplemental application. These data represent long-term controlled safety experience

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over 5 years. There were 323 patients in the finasteride group and 23 patients in the placebo group entering the fourth extension (fifth year) of the study.

The incidence of drug-related clinical adverse experiences reported by finasteride-treated patients was consistently low during Years 3 through 5, and less than 1% of finasteride-treated patients discontinued due to a drug-related adverse experience in any year.

In the first year of the Phase III studies, there were only 3 drug-related adverse experiences that occurred in $\geq 1\%$ of men: decreased libido (1.8%), erectile dysfunction (1.3%), and ejaculation disorder (1.2%). The incidence of these drug-related sexual adverse experiences declined during the course of the extension studies to $\leq 0.3\%$ for each of the above side effects, and there were no additional drug-related adverse experiences reported that occurred in $\geq 1\%$ of men receiving finasteride.

4.3 Phototrichogram Study

Treatment with finasteride was generally well tolerated. Similar numbers of men in the finasteride and placebo groups reported total (43.4% and 53.8%, respectively), drug-related (5.7% and 4.7%, respectively), and serious (0.9% and 0.9%, respectively) adverse experiences. Two men (1.9%) in the finasteride group and one (0.9%) in the placebo group reported sexual adverse experiences that were considered by the investigator to be drug related.

4.4 Phase II Open Extension Studies

Long-term (6-year and 5-year) data from these open extensions to the Phase II Pilot (Protocol 047) and Dose-Range (Protocol 081) studies confirmed the excellent safety profile of finasteride seen in the Pivotal studies and provided no evidence of an increase in the incidence of drug-related adverse experiences or identification of new adverse experiences associated with long-term treatment [P047X1; P081X1].

4.5 Safety Conclusions

1. In men with male pattern hair loss, finasteride 1 mg/day is generally safe and well tolerated.
2. The safety profile for finasteride-treated patients over 5 years is consistent with the observations on safety presented in the original New Drug Application.

5. Summary

Treatment with finasteride leads to increases in hair growth, compared with baseline, and slows the progression of hair loss. The results of the phototrichogram study suggest that the beneficial effect of finasteride on hair growth is mediated by increasing the number of actively growing hairs (anagen phase) and improving the ratio of growing hairs to resting (telogen phase) hairs. Finasteride is well tolerated and there is no evidence of an increase in the incidence of drug-related adverse experiences with long-term treatment with finasteride or identification of new adverse experiences associated with long-term treatment.

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1. Countries Where Finasteride 1 mg has Received Marketing Approval

As of 20-Feb-2001, finasteride (1-mg tablets) has received marketing approval for the treatment of male pattern hair loss in the following countries.

Table D-1

Countries Where Finasteride (1-mg) Tablets
has Received Marketing Approval for the
Treatment of Male Pattern Hair Loss

Country	Approval Date
Argentina	27-Feb-1998
Aruba	23-Feb-2000
Australia	26-Jun-1998
Brazil	29-Apr-1998
Bulgaria	14-Jul-1999
Canada	26-Jun-1998
Colombia	18-Mar-1999
Costa Rica	22-Jun-1998
Croatia	23-Nov-1998
Curacao	13-Feb-2000
Cyprus	17-Aug-1999
Czech Republic	21-Apr-1999
Chile	16-Jun-1999
Denmark	04-Nov-1998
Dominican Republic	15-Oct-2000
Ecuador	11-Aug-1998
El Salvador	02-Jun-1999
Estonia	11-Dec-1998
Finland	02-Nov-1998
France	23-Dec-1998
Germany	10-Dec-1998
Guatemala	24-Aug-1998
Honduras	25-Aug-1999
Hong Kong	02-Feb-1999
Iceland	17-May-1999
Israel	25-Aug-1998
Italy	17-Feb-1999
Jamaica	21-Oct-1999
Korea	13-Mar-2000
Kuwait	16-Mar-1999
Lithuania	27-Nov-1998
Malaysia	06-Oct-1999

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1. Countries Where Finasteride 1 mg has Received Marketing Approval (Cont.)

Table D-1 (Cont.)

Countries Where Finasteride (1-mg) Tablets
has Received Marketing Approval for the
Treatment of Male Pattern Hair Loss

Country	Approval Date
Mexico	11-Sep-1997
New Zealand	30-Nov-1997
Nicaragua	22-Jul-1999
Panama	16-Jul-1999
Peru	08-Mar-1999
Philippines	28-Jun-1999
Poland	24-Nov-1999
Portugal	28-Dec-1998
Romania	16-Jun-1998
Singapore	05-Aug-1998
Slovak Republic	28-Oct-1999
Slovenia	19-Mar-1999
South Africa	05-May-1999
Spain	02-Feb-1999
Sweden	17-Apr-1998
Switzerland	21-Oct-1998
Taiwan	08-Sep-1999
Thailand	15-Feb-1999
Trinidad/Tobago	25-Oct-1999
Turkey	29-Jan-2001
United Kingdom	20-Sep-1999
United States	19-Dec-1997
Venezuela	08-Sep-1999

2. Countries Where Finasteride 1-mg Marketing Approval has Been Withdrawn

Marketing approval of finasteride (1-mg tablets) has not been withdrawn in any country for the treatment of male pattern hair loss.

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3. Countries With Applications Pending for Finasteride 1 mg

As of 20-Feb-2001, 7 applications are pending marketing approval for finasteride (1-mg tablets) for the treatment of male pattern hair loss. The countries are listed in Table D-2.

Table D-2

Countries Where the Application is Pending

Country	Filing Date
Bolivia	21-Jul-1998
China	17-Mar-1998
Egypt	07-Jan-2000
Haiti	02-Nov-2000
Hungary	03-Jun-1997
Latvia	07-May-1998
Uruguay	23-Oct-1998

4. Countries Where the Finasteride 1-mg Application has Been Rejected

As of 20-Feb-2001, the application for finasteride (1-mg tablets) for the treatment of male pattern hair loss has not been rejected in any country.